ATTACHMENT 1
DOSE RESPONSE

1. Vaccine 1999 Feb 5;17(5):426-32
The effect of smoking on influenza, influenza vaccination efficacy and on the antibody response to influenza vaccination.
Cruijff M, Thijs C, Govaert T, Aretz K, Dinant GJ, Knottnerus A
Department of General Practice, University Maastricht, The Netherlands.

We examined the relation between cigarette smoking and (1) the occurrence of influenza, (2) the efficacy of influenza vaccination and (3) the antibody response to influenza vaccination in fifteen family practices in South-Limburg, the Netherlands, during the influenza season 1991 1992. Data were used from a randomized double-blind placebo-controlled trial into the efficacy of influenza vaccination in which smoking status was measured 10 weeks after the start of the trial. A total of 1838 subjects aged 60 years or older, of whom 1531 subjects (321 smokers, 1152 non-smokers and 58 cigar/pipe smokers) who returned the smoking questionnaire and were not previously vaccinated, were used in the analyses. The main outcome measures were serological influenza (fourfold increase of antibody titre between 3 weeks and 5 months after vaccination); clinical influenza as determined by criteria of the Dutch Sentinel Stations from self reported symptoms in postal questionnaires 10 weeks and 5 months after vaccination; increases after vaccination and decreases after 5 months in logarithmic titres of antibody against the vaccine strains. No relation between smoking and either serological or clinical influenza was found, although the risk for serological influenza was slightly (not significantly) elevated in smokers compared to non-smokers. A statistical interaction was found between smoking and vaccination when serological influenza was the outcome measure indicating that the efficacy of vaccination was greater in smokers than in non-smokers (comparison of model with and without interaction; likelihood ratio test, $p < 0.0001$). This finding is supported by a greater titre rise 3 weeks after vaccination for two out of four strains, but not by the antibody response after vaccination in previous studies on influenza and other infectious diseases. Also, this possible difference of immunogenicity is not reflected in a better protection for clinical influenza. The rise in antibody titre 3 weeks after vaccination was higher in smokers for A/Singapore/6/86 and B/Beijing/11/87, but not for the other two strains. Decline in titres after 5 months was similar for smokers and non-smokers. We conclude that smoking has no clinical or preventive significance for risk of influenza in the elderly.

Publication Types:
Clinical trial
Randomized controlled trial
PMID: 10073719, UI: 99171727

---

2. Neurology 1999 Jan 1;52(1):115-9
Smoking and Parkinson's disease: a dose-response relationship.
Gorell JM, Rybicki BA, Johnson CC, Peterson EL
Department of Neurology, Henry Ford Health System, National Institute of Environmental Health Sciences Center in Molecular and Cellular Toxicology with Human Applications, Wayne State University, Detroit, MI, USA.

OBJECTIVE: To determine whether an inverse dose-response relationship exists between cigarette smoking and PD among ever-smokers and ex-smokers. METHODS: Smoking and alcohol consumption were analyzed in 144 PD patients and 464 control subjects, who were frequency matched for sex, race, and age (+/-5 years), in a population-based case-control study of men and women > or =50 years old in the Henry Ford Health System. RESULTS: With never-smokers as the reference category, there was an inverse association between current light smokers (>0 to 30 pack-years) and PD patients (odds ratio [OR], 0.59; 95% CI, 0.23 to 1.53), and a stronger inverse association of PD with current heavy smokers (>30 pack-years; OR, 0.08; 95% CI, 0.01 to 0.62). When former >30-pack-year smokers were stratified by the interval since quitting, there was an inverse association between those who stopped >20 years ago and PD (OR, 0.86; 95% CI, 0.42 to 1.75), and a greater inverse relationship with those who stopped 1 to 20 years ago (OR, 0.37; 95% CI, 0.19 to 0.72). Alcohol consumption had no independent, significant association with PD, but heavy drinking (>10 drink-years) had a greater effect than light-moderate drinking in reducing but not eliminating the inverse association between smoking and PD. CONCLUSIONS: The inverse dose-response relationship between PD and smoking and its cessation is unlikely to be due to bias or confounding, as discussed, providing indirect evidence that smoking is biologically protective.
PMID: 9921857, UI: 99118830

---

3. J Intern Med 1998 Sep;244(3):227-34
Humoral immune response to Chlamydia pneumoniae in twin discordant for smoking.
von Hertzen L, Kaprio J, Koskenvuo M, Isoaho R, Saikku P
The Finnish Lung Health Association, Helsinki.

OBJECTIVES: The aim of this study was to investigate whether there is a relationship between smoking and Chlamydia pneumoniae specific antibody levels in generally healthy subjects, and whether this possible relationship is dose-dependent. DESIGN: Match pair study. SUBJECTS: The study population comprised of 111 same-gender twin pairs from the Finnish Twin Cohort who in a previous study reported the highest discordance between smoking assessed as pack-years. MAIN OUTCOME MEASURES: Smoking and background data were obtained by a questionnaire, and C. pneumoniae specific serum IgG and IgA antibodies were measured by the micro-immunofluorescence (mIF) test. RESULTS: A significantly higher proportion of men with a history of smoking had elevated levels (a titre of > or=40) of serum IgA antibodies (P=0.003), whereas in women, a significant difference between the pairs was found in the proportion of IgG seropositive (a titre of > or=128) subjects (P=0.03). Conditional logistic regression analysis

revealed that the risk for elevated IgA antibodies suggestive of chronic infection was significantly increased in current or former smokers in men (odds ratio 5.0 with 95% confidence intervals of 1.45-17.3). No dose-response effect was found between smoking and IgG or IgA titres, neither even if men and women were analysed separately. CONCLUSION: Smoking was significantly associated with elevated IgA antibody levels in men, supporting indirectly the hypothesis that smoking is a contributory factor in the establishment of chronic C. pneumoniae infection.
PMID: 9747745, UI: 98418517

---

4. Prev Med 1998 May-Jun;27(3):337-47
The degree and type of relationship between psychosocial variables and smoking status for students in grade 8: is there a dose-response relationship?
Pederson LL, Koval JJ, McGrady GA, Tyas SL
Department of Community Health and Preventive Medicine, Morehouse School of Medicine, Atlanta, Georgia 30310, USA. lindap@mindspring.com

BACKGROUND: While most research focuses on simply analyzing the differences between smokers and non-smokers, dose-response analyses may be used to find evidence of the nature of the association between psychosocial variables and involvement with smoking in adolescence. METHODS: For the study, 1,614 grade 8 students from Scarborough, Ontario, Canada, completed a self-administered questionnaire that included items on sociodemographic characteristics, experience with smoking, lifestyle, health and weight, work status, and social involvement as well as parental education, occupation, and family and peer smoking. A series of scales measuring self-esteem, stress, coping, social support, mastery, social conformity, and rebelliousness was incorporated. RESULTS: Dose-response relationships were evidenced for all categories of variables and were demonstrated for the total group and, in most cases, for males and females when analyzed separately. CONCLUSIONS: Relationships between variables are not "all or none," but may vary depending on amount or level of other factors. These relationships provide insight into the mechanisms underlying initiation to, maintenance of, and cessation of smoking and should be taken into account in programs to reduce or prevent adolescent tobacco use.
PMID: 9612824, UI: 98275771

---

5. Health Phys 1997 Dec;73(6):899-905

Multifactorial analysis of lung cancer dose-response relationships for workers at the Mayak nuclear enterprise.

Tokarskaya ZB, Okladnikova ND, Belyaeva ZD, Drozhko EG
Clinical Department, Biophysical Institute, Ozersk, Russia.

Dose-response relationships for alpha-radiation-induced lung cancers (adenocarcinoma, squamous carcinoma and small cell carcinoma) were developed by multifactorial analysis using data for Mayak nuclear enterprise workers chronically exposed by inhalation to 239Pu. The three most important lung cancer risk factors (smoking, plutonium incorporation, and external gamma irradiation), out of six factors previously identified, were used. Relative risks (odds ratios) were determined for 500 nuclear enterprise workers (162 cancer cases, 338 control) for different dose levels using a case-control study design and logistic regression. A threshold at about 3.7 kBq or 0.80 Gy was discovered for incorporated plutonium, which is satisfactorily described by linear-quadratic and quadratic models. Excess relative risk was 0.020 kBq(-2) and 0.97 Gy(-2). This quadratic function was mainly due to adenocarcinoma. A trend for decreasing risk was noted for the lowest levels of plutonium incorporation, near permissible level. No clear-cut dose-response relationship for lung cancer induction by chronic external gamma irradiation was obtained. Lung cancer induction by cigarette smoking had a linear dependence: smoking of one pack of papiroses (a type of Russian cigarette) per day for 5 y increases the lung cancer risk twofold. The effect was most clearly manifested for squamous-cell carcinoma.

Comment in: Health Phys 1998 Jun;74(6):726-8
PMID: 9373067, UI: 98038904

---

6. Crit Rev Oral Biol Med 1997;8(4):437-60

Tobacco and smoking: environmental factors that modify the host response (immune system) and have an impact on periodontal health.

Barbour SE, Nakashima K, Zhang JB, Tangada S, Hahn CL, Schenkein HA, Tew JG
Clinical Research Center for Periodontal Diseases, School of Dentistry, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298-0566, USA.

This review summarizes the current data on the effects of smoking and tobacco on the immune system and its potential impact on periodontal health. Smokers are 2.5-6 times more likely to develop periodontal disease than non-smokers, and there is evidence for a direct correlation between the number of cigarettes smoked and the risk of developing disease. Tobacco users also tend to exhibit increased severity of periodontal disease. Direct correlations between tobacco use and increased attachment loss and pocket depth and reduced bone crest height have been reported. Although the correlation between tobacco use and periodontal disease is quite strong, the role of tobacco in the pathogenesis of periodontal disease is uncertain. Recent studies indicate that one potential mechanism is that tobacco use exacerbates periodontal disease because it alters the immune response to periodontal pathogens. Indeed, smokers exhibit increased numbers of peripheral blood mononuclear phagocytes which appear to be functionally compromised. Inadequate phagocyte activity could reduce the clearance of pathogens from the oral cavity and thereby facilitate the development of periodontal disease. Tobacco-exposed B- and T-lymphocytes exhibit reduced proliferative capacities which could limit the production of protective immunoglobulins against oral pathogens. The risk factors for periodontal disease can be broadly classified as genetic, environmental, host-response factors, and host-related factors such as age. Tobacco, an environmental factor, undermines the host response and may facilitate the development and progression of periodontal disease. This review highlights the inter-relatedness of two of the risk factors associated with periodontal disease.

Publication Types:
Review
Review, tutorial
PMID: 9391754, UI: 98053242

J Natl Cancer Inst 1998 Oct 7;90(19):1440-50

Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe.

Boffetta P, Agudo A, Ahrens W, Benhamou E, Benhamou S, Darby SC, Ferro G, Fortes C, Gonzalez CA, Jockel KH, Krauss M, Kreienbrock L, Kreuzer M, Mendes A, Merletti F, Nyberg F, Pershagen G, Pohlabeln H, Riboli E, Schmid G, Simonato L, Tredaniel J, Whitley E, Wichmann HE, Saracci R, et al
International Agency for Research on Cancer, Lyon, France. boffetta@iarc.fr

BACKGROUND: An association between exposure to environmental tobacco smoke (ETS) and lung cancer risk has been suggested. To evaluate this possible association better, researchers need more precise estimates of risk, the relative contribution of different sources of ETS, and the effect of ETS exposure on different histologic types of lung cancer. To address these issues, we have conducted a case-control study of lung cancer and exposure to ETS in 12 centers from seven European countries. METHODS: A total of 650 patients with lung cancer and 1542 control subjects up to 74 years of age were interviewed about exposure to ETS. Neither case subjects nor control subjects had smoked more than 400 cigarettes in their lifetime. RESULTS: ETS exposure during childhood was not associated with an increased risk of lung cancer (odds ratio [OR] for ever exposure = 0.78; 95% confidence interval [CI] = 0.64-0.96). The OR for ever exposure to spousal ETS was 1.16 (95% CI = 0.93-1.44). No clear dose-response relationship could be demonstrated for cumulative spousal ETS exposure. The OR for ever exposure to workplace ETS was 1.17 (95% CI = 0.94-1.45), with possible evidence of increasing risk for increasing duration of exposure. No increase in risk was detected in subjects whose exposure to spousal or workplace ETS ended more than 15 years earlier. Ever exposure to ETS from other sources was not associated with lung cancer risk. Risks from combined exposure to spousal and workplace ETS were higher for squamous cell carcinoma and small-cell carcinoma than for adenocarcinoma, but the differences were not statistically significant. CONCLUSIONS: Our results indicate no association between childhood exposure to ETS and lung cancer risk. We did find weak evidence of a dose-response relationship between risk of lung cancer and exposure to spousal and workplace ETS. There was no detectable risk after cessation of exposure.

Publication Types:
Multicenter study
Comments:
Comment in: J Natl Cancer Inst 1998 Oct 7;90(19):1416-7
Comment in: J Natl Cancer Inst 1999 Mar 17;91(6):560-1
PMID: 9776409, UI: 98447304